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10/508,759	09/22/2004	Hyo Jeong Hong	DE1586	9699

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EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	PAPER NUMBER
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,759	HONG ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-24* is/are pending in the application.

4a) Of the above claim(s) *11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6,7 and 10* is/are rejected.

7)☒ Claim(s) *3-5,8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/2006 and 6/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received December 21, 2007.

Election/Restrictions

Applicant's election without traverse of group I, claims 1-10 is acknowledged. Claims 11-24 are withdrawn because the claims are drawn to the non-elected invention. Claim 1 was canceled. Claims 2-10 are under examination in the present Office Action.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

Acknowledgment is made for priority to a PCT//KR03/00564 and foreign priority to the Korean Patent 10-2002-0015708. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites "(…) murine monoclonal antibody variable regions **of** hepatitis B virus pre-S1 antigen (…)". This recitation is incorrect. The specification discloses that the variable

region of the murine monoclonal antibody bind to HBV pre-S1 antigen. Thus it is suggested that the claim is amended to recite: "murine monoclonal antibody variable regions **that bind** hepatitis B virus pre-S1 antigen". Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 7, and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present claims are drawn to a method of preparing humanized antibody by grafting murine monoclonal antibody KR127 into the human antibody heavy chain DP-JH4 and light chain DPH12-JK4.

It is acknowledged that Applicants provided the amino acid sequences for the CDRs of murine KR127 antibody. Thus the Application provides sufficient disclosure in order for the skilled artisan to use the CDRs from the KR127 antibody as required by the claims. However neither the information with regard to the Biological Deposit of the hybridoma cell lines producing antibodies DP-JH4 and DPH12-JK4 nor the specific sequences for the human antibody heavy DP-JH4 and light chain DPH12-JK4, or plasmids carrying the said sequences can be found in the present specification or in the sequence listing. It appears that antibodies DP-JH4 and DPH12-JK4 or plasmids carrying heavy DP-JH4 and light chain DPH12-JK4 are not readily available material. Generating the exact same antibodies or plasmids carrying the heavy DP-JH4

and light chain DPH12-JK4 is not a reproducible process and therefore the specification does not adequately teach how to make and use the claimed invention. The enablement requirement of 35 U.S.C. § 112, first paragraph, may be satisfied by either 1) the disclosure and submission of the amino acid or nucleic acid sequences encoding the heavy DP-JH4 and light chain DPH12-JK4, 2) a Biological Deposit of plasmids carrying the heavy DP-JH4 and light chain DPH12-JK4, 3) or Biological Deposit of the hybridoma cell lines producing the antibodies DP-JH4 and DPH12-JK4.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Leong et al. (Cytokine, November 2001, Vol. 16, p. 106-119).

Claims are drawn to a process for preparing a humanized antibody comprising the steps of: replacing each amino acid residue in the complementarity determining region (CDR) of murine monoclonal antibody heavy and light chain variable regions with alanine to produce transformants; selecting a transformant that has a lower affinity to the human antigen (Kd) than the original murine antibody; determining the replaced amino acid residues of said transformant as a specificity determining residue (SDR), and grafting said SDR to at least one of the corresponding amino acid residues into human antibody variable regions.

Claim 2 is interpreted as being broadly drawn to a method of preparing any humanized antibody comprising the steps of replacing each amino acid residue in the CDR of any murine monoclonal antibody with alanine.

Leong et al. disclose a method of preparing humanized anti-IL-8 antibody comprising performing alanine scanning mutagenesis of the murine CDRs, selecting alanine substituted amino acid positions that contribute to the binding to human IL-8 (thereby determining the specificity binding residues) and grafting the alanine substituted CDR regions of the murine anti-IL-8 antibody onto the human IgG framework (see the entire document, particularly Alanine scanning mutagenesis on page 108, Experimental procedures: Construction of humanized version of anti-IL-8 antibody 6G4.2.5, and Tables 1 and 2). It is noted that the step of "replacing each amino acid residue in the CDR region of murine monoclonal antibody" is commonly referred to in the art as: "alanine scanning mutagenesis". The present specification uses the term "alanine scanning mutagenesis" when discussing the steps of the present method (see [0026]). Thus because Leong et al. discloses the step of performing alanine scanning mutagenesis of the variable light and heavy chain of the murine antibody, Leong et al. disclose the present method step of replacing each amino acid residue in the CDR region of murine monoclonal antibody. Thus Leong et al. anticipate the present claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 3 is rejected under 35 U.S.C. 103(a) as being obvious over Maeng et al. (Virology, 2000 Vol. 270, p. 9-16) in view of Leong et al. (Cytokine, November 2001, Vol. 16, p. 106-119).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 3 is drawn to a process of preparing a humanized antibody comprising the steps of: replacing each amino acid residue in the complementarity determining region (CDR) of murine monoclonal antibody heavy and light chain variable regions with alanine to produce transformants; selecting a transformant that has a lower affinity to the human antigen (Kd) than the original murine antibody; determining the replaced amino acid residues of said transformant as a specificity determining residue (SDR), and grafting said SDR to at least one of the

corresponding amino acid residues into human antibody variable regions. The CDR regions are selected from HCDR1, HCDR2 and HCDR3 of the heavy chain represented by SEQ ID NO: 2, and LCDR1, LCDR2 and LCDR3 of the light chain represented by SEQ ID NO: 4 of the murine antibody.

It is noted that claim 3 does not recite the name of the murine monoclonal antibody used in the methods of the present invention. Based on Applicant's disclosure it is understood that the heavy chain of SEQ ID NO: 2 and the light chain of SEQ ID NO: 4 are the heavy and light chains from the **KR127** antibody. It is assumed that the KR127 antibody has been publicly available at the time of Maeng's et al. (Virology, 2000 Vol. 270, p. 9-16) publication and thus at the time of the invention because KR127 antibody has been disclosed in other prior art publications such as for example the KR127 antibody is disclosed in US Patent 7,115,723 B1.

Maeng et al. teach the murine monoclonal antibody KR127 (see the entire document, particularly pages 10-14, Figures 1 and 6). Maeng et al. do not teach the heavy and light chain sequences of the KR127 antibody, however the heavy chain of SEQ ID NO: 2 and the light chain of SEQ ID NO: 4 are inherent properties of the KR127 antibody disclosed by Maeng et al. The CDR regions recited in claim 3, the heavy chain HCDR1 (aa 31-35), HCDR2 (aa 24-34) and HCDR3 (aa 95-102) and light chain LCDR1 (aa 24-34), LCDR2 (aa 50-56) and LCDR3 (aa 89-97) are inherently present in the KR127 antibody disclosed by Maeng et al.

Thus it is the Office's position that murine monoclonal antibody comprising the heavy and light chain of SEQ ID NO: 2, SEQ ID NO: 4 of the present invention has the same structure and function as the KR127 antibody disclosed in the prior.

Maeng et al. teach replacing the amino acids within the CDRs of the KR127 antibody with alanine (see page 13 and 14). Maeng et al. do not teach humanizing the KR127 antibody. Leong's teach humanizing a murine antibody by grafting the alanine substituted CDR onto the human IgG framework to prevent development of human anti-mouse antibodies (HAMA) in humans treated with KR127.

It would have been *prima facie* obvious to the person of ordinary skill in the art to humanize the KR127 antibody in order to prevent development of human anti-mouse antibodies (HAMA) in humans treated with KR127.

One would have been motivated to humanize Maeng's KR127 antibody by grafting the alanine substituted KR127 SDRs to onto the human antibody heavy and light chain framework because murine antibodies designed for human use must be humanized in order to prevent development of human anti-mouse antibodies (HAMA).

One would have had a reasonable expectation of success to practice the present method because the methods of performing alanine scanning mutagenesis and grafting the alanine substituted CDR residues onto the human antibody framework are well established in the art as evidenced by Leong et al.

Thus the present methods would have been *prima facie* obvious to the skilled artisan at the time when the invention was made.

Claim Objection

Claims 4, 5, 8, and 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen, Ph.D./
Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648